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The Pulmonary First-pass Uptake of Five Nondepolarizing Muscle Relaxants in the Pig

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Background: **It is not known whether the lungs influence the early pharmacokinetics of muscle relaxants and, if they do, whether differences in pulmonary uptake contribute to the differences in potency and/or onset time among muscle relaxants. Because the lungs are uniquely positioned, receive the entire cardiac output, have a large capillary surface area, and can temporarily store various basic drugs, the authors determined whether substantial pulmonary first-pass uptake of muscle relaxants occurs.**

Methods: **In 14 pigs, rocuronium, vecuronium, Org 9487, Org 7617, or *d*-tubocurarine were administered simultaneously with indocyanin green within 1 s into the right ventricle, and then arterial blood was sampled every 1.2 s (in the first min). The tibialis muscle response was registered mechanomyographically.**

Results: **The maximum block was 93% (68–100% [median and range]). Onset times ranged from 83 s (78–86 s) for rocuronium to 182 s (172–192 s) for *d*-tubocurarine. Fraction-*versus*-time outflow curves showed that the peak of muscle relaxants and indocyanin green occurred almost simultaneously. Pulmonary first-pass retention was negligible. The retention of muscle relaxants at 95% passage of indocyanin green was −9% (−31 to 18%). The difference in the mean transit time between muscle relaxant and indocyanin green was 1.0 (0.8 to 1.4), 0.2 (−0.8 to 0.3), 0.3 (0.2 to 0.4), 0.5 (0.2 to 1.3), and −2.2 s for rocuronium, vecuronium, Org 9487, Org 7617, and *d*-tubocurarine, respectively.**

Conclusions: **There is no substantial pulmonary first-pass uptake of rocuronium, vecuronium, Org 9487, Org 7617, or *d*-tubocurarine in pigs. Therefore, differences in pulmonary first-pass uptake do not contribute to the differences in potency and/or onset time among muscle relaxants. (Key words: Onset time; pharmacokinetics; plasma concentration; potency.)**

AFTER intravenous administration, drugs must pass the lungs to reach the arterial circulation. It is not known whether the lungs influence the early pharmacokinetics of muscle relaxants and, if they do, whether differences in pulmonary uptake contribute to the differences in potency and/or onset time among muscle relaxants. So far, our knowledge of the role of the lungs in the pharmacokinetics of muscle relaxants is confined to the results of a study by Cohen *et al.*[1] in 1968. They used whole-body autoradiography of the rat and found high initial concentrations of *d*-tubocurarine, gallamine, and decamethonium in the lung.

For several reasons the lungs might be able to influence the early pharmacokinetics of muscle relaxants. Not only are the lungs interposed between the site of drug administration and the site of effect, but they also receive the entire cardiac output and are equipped with the largest capillary surface area in the body (126 ± 12 m^2).[2] Because the lung receives the entire cardiac output, even a small pulmonary extraction ratio could account for a significant clearance. Furthermore, the lungs have been shown to (temporarily) store various basic drugs,[3–7] including opioids[8–12] and propofol.[13,14] Because muscle relaxants are basic amines, it is possible that also muscle relaxants undergo pulmonary uptake.

Therefore, we posed two questions: Is there substantial pulmonary first-pass uptake of muscle relaxants? If there is, do muscle relaxants that differ in potency also differ in pulmonary first-pass uptake? To answer these questions, we evaluated the pulmonary first-pass uptake of five muscle relaxants in the pig.

Methods

Preliminary Preparation

With the approval of the Ethical Committee on Animal Experiments of the Faculty of Medical Sciences, Gro-

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ningen, The Netherlands, we studied 14 male pigs (Yorkshire F_1 hybrid; body weight, 20–27 kg). After a fasting period of 16 h with free access to water, the pigs were anesthetized intramuscularly with midazolam (15 mg) and ketamine (500 mg). After the pigs were weighed, an ear vein was cannulated and infusions of pentobarbitone sodium (5 mg · kg^{-1} · h^{-1}), morphine (0.1 to 0.2 mg · kg^{-1} · h^{-1}), and isotonic glucose in saline (2 ml · kg^{-1} · h^{-1}) were started. If necessary, the pentobarbitone sodium infusion rate was adjusted to maintain an adequate depth of anesthesia. The pig's trachea was intubated and the lungs were artificially ventilated with air using a Cameco UV 705 (Cameco, Sweden) respirator (frequency, 24 breaths/min; pressure, 20 cm water). The end-tidal carbon dioxide pressure was maintained between 30 and 38 mmHg (Godart Capnograph Mark 11; E. Jaeger, Wuerzberg, Germany). To document the *p*H value and to have a parameter for both lung function and ventilation, arterial blood gas analysis was performed at intervals. Heart rate (B-1200 Biotachometer, MS 35; Electrodyne Co., Inc., USA) and rectal temperature were measured continuously, and temperature was maintained at 38°C using a heating blanket.

The right femoral vein was cannulated to allow previously withdrawn blood to be returned to compensate for the sampling volume. The right femoral artery was cannulated (ID, 2.6 mm) for rapid blood sampling, and the left axillary artery was fitted with a catheter to measure blood pressure (Statham P23DB; KWS 3005 HSE Electro-Manometer). After a small skin incision was made, a flow-directed catheter (Baxter-Edwards 93A-131H-7F; Baxter Edwards Healthcare Corporation, Irvine, CA) was introduced *via* the right internal jugular vein into the pulmonary artery and positioned according to changes in pressure waveform. Cardiac output was measured through thermodilution (WTI MC401; WTI Holland) at regular intervals. To administer indocyanin green (ICG) and muscle relaxants, the pulmonary artery catheter was withdrawn until its tip was in the right ventricle.

The left common peroneal nerve was exposed and two silver stimulation electrodes were attached. The nerve was ligated proximal to the electrodes to prevent repetitive backfiring. After the overlying skin was closed, the nerve was stimulated supramaximally with square-wave stimuli lasting 0.2 ms at a frequency of 0.1 Hz (Grass S 88; Grass Instruments, Quincy, MA). The response of the tibialis anterior muscle was registered mechanomyographically using a force transducer (LB 8000 25N; Maryland Instruments Ltd., Maywood, USA) connected to a muscle relaxation monitor MK 11 and to a recorder (MT 9500; Astro-Med, Rhode Island). Preload was measured continuously and kept constant at approximately 400 g. The muscle response was allowed to stabilize during a period of 30 min after the preparation. After the tibialis muscle was prepared, 180 ml blood was removed from each pig through the right femoral artery cannula and anticoagulated (300 IU heparin). During and immediately after blood was withdrawn, 600 ml saline, 0.9%, was administered in 30 min. Twenty milliliters of arterial blood was withdrawn in a heparin-prepared tube to construct calibration curves of ICG and the muscle relaxant. A calibrated roller pump (coronary pump unit, Dreissen, Holland) was interposed between the femoral artery and a fraction collector (FRAC 200; Pharmacia LKB). The volume of the connecting tubing between the femoral artery, roller pump, and fraction collector was such that with a flow of the roller pump of 180 ml/min, the time for the blood to reach the collecting tubes was 6 s. At the end of the experiments, pigs received an overdose of pentobarbitone sodium until circulatory arrest occurred.

Experimental Protocol

Based on differences in potency and onset time in the pig, equipotent doses of vecuronium (0.1 mg/kg), rocuronium (0.6 mg/kg), Org 9487 (0.37 mg/kg), Org 7617 (0.96 mg/kg), and *d*-tubocurarine (0.03 mg/kg) were given. Pigs were randomized according to the muscle relaxant they received using the roll of a die. Each pig received only one muscle relaxant. A neuromuscular block between 70% and 95% was pursued.

At a stable muscle response and immediately before the experiment, a fresh solution of ICG was made by adding 10 ml aqueous diluent to a 50-mg vial, which was mixed carefully. The dose of ICG was 5 mg. The syringes containing ICG or muscle relaxant were weighted before and after placement of their content in a small-bore cannula (volume, 3.2 ml) connected with one side to the distal port (which ended in the right ventricle) of the pulmonary artery catheter, and with the other side connected to a 10-ml syringe filled with normal saline.

At time zero, the roller pump and the fraction collector were started. Six seconds later, the ICG and the muscle relaxant were injected progressively in 1 s into the distal port of the pulmonary artery catheter and flushed with 10 ml normal saline. During the sampling phase (20 min), the previously withdrawn 180 ml blood was reinfused to replace the blood lost by sampling and to maintain hemodynamic stability.

Femoral arterial blood was sampled every 1.2 s (min

1), every 6 s (min 2), every 15 s (min 3–6), every 30 s (min 7–10), and every 2 min (min 11–20) after administration of ICG and/or the muscle relaxant. Samples were taken during the first min using the roller pump and fraction collector. Thereafter, sampling was performed manually using a three-way stopcock. After blood was collected into heparin-prepared tubes and centrifuged (at 2,100 *g* for 10 min), the part of the sample that was used to determine the muscle relaxant was acidified with 1 M NaH_2PO_4 to prevent hydrolysis of the muscle relaxants and stored at − 18°C until it was needed for analysis.

Determination of Muscle Relaxant in Plasma

Determination of the muscle relaxants in plasma was carried out by high-performance liquid chromatography using postcolumn ion-pair extraction and fluorimetric determination. The method has been described for rocuronium[15] and was adapted and validated for the other muscle relaxants and the active (3-OH) metabolites of vecuronium, Org 9487 and Org 7617. As internal standards, we used di-OH vecuronium for the determination of rocuronium, di-OH Org 7617 for vecuronium and 3-OH vecuronium, rocuronium for *d*-tubocurarine, 3-OH Org 7617 for Org 9487 and 3-OH Org 9487, and 3-OH Org 9453 for Org 7617 and 3-OH Org 7617.

After a liquid–liquid ion-pair extraction of the biologic matrix, the samples were subjected to chromatography on a reversed-phase high-performance liquid chromatography column, using an aqueous buffer-dioxane as the mobile phase (84:16 vol/vol for rocuronium, vecuronium, and 3-OH vecuronium; 85:15 vol/vol for *d*-tubocurarine; 82:18 vol/vol for Org 9487 and 3-OH Org 9487; and 81:19 vol/vol for Org 7617 and 3-OH Org 7617). The aqueous buffer consisted of 0.1 M sodium dihydrogen phosphate, 0.11 mM heptane sulphonic acid, and 0.11 mM 9,10-dimethoxyanthracene-2-sulphonate for rocuronium, vecuronium, Org 9487, and Org 7617, whereas 0.15 mM NaH_2PO_4 and 0.33 mM 9,10-dimethoxyanthracene-2-sulphonate were used for *d*-tubocurarine. After separation, the eluent was extracted with dichloroethane and the organic phase was led to a fluorimetric detector operating at 385-nm excitation and 452-nm emission.

For each agent, the method showed a linear relation between the logarithm of the injected amount of drug and the logarithm of the response ratio in a range of at least 10 to 1,000 ng in the prepared samples, obtained from 10 to 1,000 μl plasma.

The mean precision, expressed in the coefficients of variation of the intraday variability and in the coefficients of variation of the accuracy data, was 6% for rocuronium and *d*-tubocurarine, 7% for vecuronium, 6% for 3-OH vecuronium, 9% for Org 9487, 7% for 3-OH Org 9487, 7% for Org 7617, and 4% for 3-OH Org 7617.

The mean absolute deviation of the accuracy samples covering the concentrations of the unknown samples was 6% for rocuronium, 9% for Org 9487 and Org 9488, 8% for *d*-tubocurarine, 4% for vecuronium, 8% for 3-OH vecuronium, 9% for Org 7617, and 3% for Org 9522.

The lower limit of quantification, defined as the minimum concentration that could be detected with a precision and accuracy greater than 15%, was 50 ng/ml for rocuronium, Org 9487, Org 9488, Org 7617, and Org 9522; 25 ng/ml for vecuronium and 3-OH vecuronium; and 20 ng/ml for *d*-tubocurarine.

Three of the five muscle relaxants have pharmacologically active metabolites. To compensate for the metabolites, the amounts of the metabolites measured in the samples were added to the amounts of parent compounds under correction for the difference in molecular weight.

Determination of Indocyanin Green in Plasma

Immediately after the experiment, plasma ICG concentrations were measured in all samples by direct spectrophotometric assessment at 805 nm (PU 8740 UV/VIS; Philips, The Netherlands). To construct the calibration line, 1 ml (5 mg) from the ICG vial used in the same experiment was mixed in graded amounts with arterial plasma of the same animal drawn before the experiment began. The relation between concentration and extinction was slightly curvaceous. After logarithmic transformation of both axes, linear calibration curves were obtained (R^2 = 0.994 [0.989 to 0.999]). For each experiment the peak and trough ICG values were determined by measuring the extinction in the range from 770 to 920 nm (peak, 805; trough, 900 nm). To allow correction of the extinction at 805 nm for blank density,[16] the absorption at 900 nm was measured in all samples.

Calculation of Pulmonary First-pass Uptake

Pulmonary first-pass uptake is defined as the loss of drug from blood after a single passage through the lung, and it is the net result of uptake of the drug into lung tissue or adhesion of drug to lung vasculature and back diffusion of the drug from lung tissue or vasculature into the blood.

The pulmonary first-pass uptake of the muscle relaxant

was determined with the double-indicator dilution method, as described by Bertler *et al.*[17] and modified by Jorfeldt *et al.*[3] and Roerig *et al.*[11] Briefly, ICG (Cardio-Green, Becton Dickinson Microbiology Systems, Cockeysville, USA) was used as the nonextractable vascular indicator and was administered simultaneously with the muscle relaxant into the right ventricle. To calculate the first-pass pulmonary extraction, the first-pass pulmonary retention, and the mean transit time (MTT), the concentrations (C) of ICG and the muscle relaxant in arterial plasma were normalized by expressing them as a fraction (F) of the administered dose (D); that is, F = C/D. Paired ICG and muscle relaxant outflow curves of these fractions were constructed as a function of time. Because the extraction, retention, MTT, and the cardiac output were calculated for the first-pass of the ICG and muscle relaxant through the lungs, the fraction-*versus*-time curves were corrected for recirculation by log-linear extrapolation of the linear descending part of the curve.

Extraction is defined as the percentage of the concentration of the muscle relaxant that is removed instantaneously by the lung tissue and vasculature from the blood. Extraction was calculated according to Geddes *et al.*,[18] where F_t is the fraction at time t:

$$\text{Extraction}_t(\%) = \left(1 - \frac{F_{t,\ \text{MUSCLE RELAXANT}}}{F_{t,\ \text{ICG}}}\right) \times 100$$

Retention is defined as the percentage of the administered dose of the muscle relaxant that is retained in the lungs. Retention was calculated according to the method of Bertler *et al.*,[17] were the AUC is the area under the fraction-*versus*-time curve (the AUC was calculated according to the trapezoidal rule method):

$$\text{Retention}_t(\%) = \left(1 - \frac{AUC_{t,\ \text{MUSCLE RELAXANT}}}{AUC_{t,\text{ICG}}}\right) \times 100$$

In addition, the retention of the muscle relaxant when 95% of the ICG had passed the lungs was calculated, as described by Bertler *et al.*[17]

The MTT is defined as the mean time a drug molecule needs to travel from the site of administration (right ventricle) to the site of sampling (femoral artery). The MTT was calculated from the AUC and the AUMC. AUMC is the area under the first moment of the fraction-*versus*-time curve. The first moment results from the product of fraction (F) and time (t):

$$\text{Mean Transit Time(s)} = \frac{AUMC_{\text{ICG or MUSCLE RELAXANT}}}{AUC_{\text{ICG OR MUSCLE RELAXANT}}}$$

The cardiac output was measured using thermodilution and calculated[19] from

$$\text{Cardiac Output } (\text{l.min}^{-1}) = \frac{\text{Dose}_{\text{ICG}}}{AUC_{\text{ICG}}}$$

Statistics

All data are expressed as the median ± range, unless stated otherwise. Data were analyzed using a Wilcoxon rank sum test (matched pairs). A P value < 0.05 was considered significant.

Results

Body weights of pigs were similar among muscle relaxants. The degree of maximum block was 93% (68–100%). The onset times of neuromuscular block (time elapsed between end of administration of muscle relaxant and peak effect) were 83 s (78–86 s), 66 and 85 s, 88 s (85–107 s), 84 s (69–111 s), and 182 s (172–192 s) for rocuronium, vecuronium, Org 9487, Org 7617, and *d*-tubocurarine, respectively. In one experiment with vecuronium, the time to peak effect could not be measured because the block was 100%, which was reached after 49 s.

In all experiments, the concentrations of muscle relaxant and ICG in arterial plasma were, at least during the first 10 min of sampling, much greater than the lower limit of quantification. The amounts of metabolites in the samples were small and always less than 15% of that of the parent compound.

Simultaneously, a high peak in the fraction of ICG and in the fraction of the muscle relaxants occurred between 13 and 20 s after administration of ICG and muscle relaxant in all experiments (fig. 1). Because the cardiac output was different for each pig and cardiac output affects the height and shape of the peak, it is not possible to express the fractions of ICG and muscle relaxant *versus* time as the mean for all pigs that received the same muscle relaxant. Therefore, the fractions in figure 1 are from single pigs representing the curve observed for that muscle relaxant. The increase, the decrease, and the peak of the fractions of ICG and muscle relaxant occurred at the same time or within 2.4 s of each other. In all experiments, the initial high peaks were followed by a smaller peak between approximately 28 and 32 s, representing the second pass of ICG and muscle relaxant through the lung.

The first-pass pulmonary extraction showed a similar

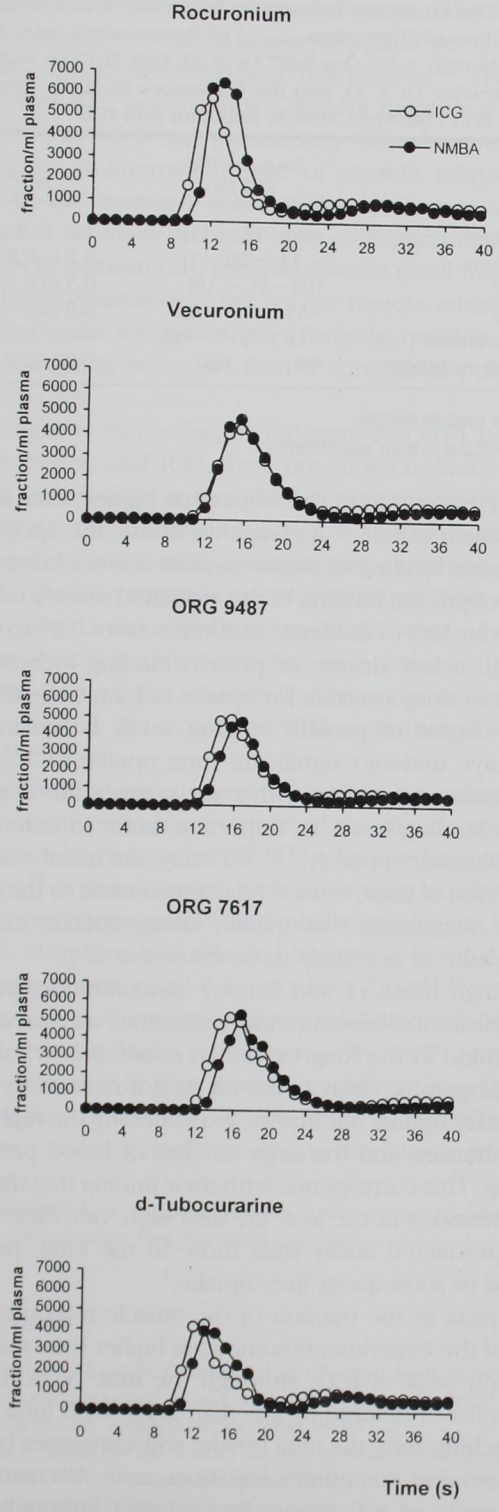

Fig. 1. Typical examples of fraction-*versus*-time outflow curves of indocyanin green and rocuronium, vecuronium, Org 9487, Org 7617, or *d*-tubocurarine. The fraction is the arterial plasma concentration (expressed as ng/ml) divided by the dose (ng). Time zero is end of administration of indocyanin green and the muscle relaxant (NMBA).

pattern in all experiments. An initial extraction of 100% (50–100%) decreased to approximately zero within 5.2 s, became negative or varied at approximately zero, and was 16% (−59 to 38) just before recirculation.

Figure 2 shows the first-pass pulmonary retention of each muscle relaxant. Table 1 reports the first-pass pulmonary retention when 95% ICG had passed for each muscle relaxant. In all experiments, 95% of the AUC of ICG was reached before recirculation of the muscle relaxant was observed.

The MTTs were 15.4 s (14.4 to 17.2 s), 16.9 s (15.5 to 21 s), 17.2 s (13.1 to 17.8 s), 17.2 s (16.4 to 18.7 s), and 12.7 s (13.3 s) for rocuronium, vecuronium, Org 9487, Org 7617 and *d*-tubocurarine, respectively. The differences in MTTs between muscle relaxants and ICG are reported for each muscle relaxant in table 1. The cardiac output determined with thermodilution (2.7 l/min [1.7 to 3.5]) corresponded with the cardiac output determined by ICG dilution (2.2 l/min [1.7 to 3.7], $P = 0.65$).

Discussion

There is no substantial pulmonary first-pass uptake of rocuronium, vecuronium, Org 9487, Org 7617, or *d*-tubocurarine in pigs. Therefore, differences in pulmonary first-pass uptake do not contribute to the differences in potency and/or onset time among muscle relaxants.

The similarity in timing and configuration between the fraction-*versus*-time curves of ICG and those of the muscle relaxants, the negligible pulmonary retention when 95% of the ICG had passed, and the similar MTTs for ICG and the muscle relaxants show the absence of substantial pulmonary first-pass uptake of these muscle relaxants. In other words, the lungs do not influence the height or time course of the peak concentration of the muscle relaxant in arterial plasma in a manner different from that of ICG. Because we selected muscle relaxants that differ in potency by a factor of 30 and in onset time by a factor of 2, this study shows that differences in potency and onset time cannot even be explained in part by differences in pulmonary first-pass uptake. In general, muscle relaxants do not have physiochemical properties suited for uptake in tissue. Roerig *et al.*[4,11] showed that, in particular, basic amines with a moderate to high lipophilicity are taken up to a large extent during their first pass through the lungs. Although the muscle relaxants studied are all basic amines, the lipophilicity of the evaluated muscle relaxants is low, with octanol–Krebs partition coefficients between 0.16 and 1.05,

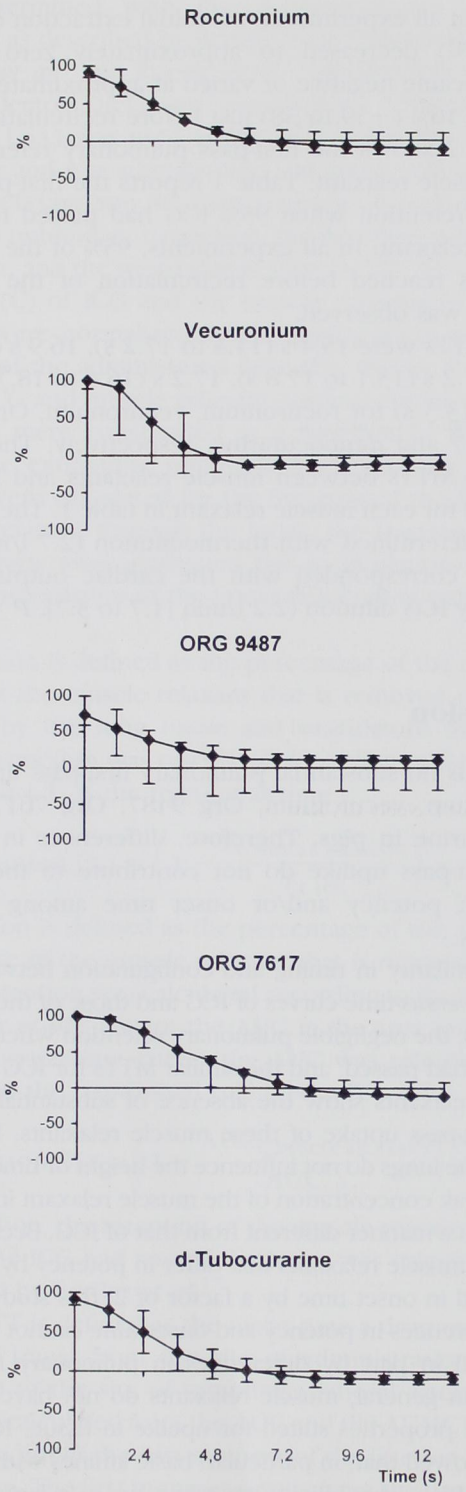

Fig. 2. Pulmonary first-pass retention of rocuronium, vecuronium, Org 9487, Org 7617, and *d*-tubocurarine. Retention is the percentage of the administered dose of the muscle relaxant that is retained in the lungs. Time zero is the time of first appearance of indocyanin green in arterial plasma. Time 13.2 s is the average time at which 95% of indocyanin green had passed (median [range]).

Table 1. The First-pass Pulmonary Retention When 95% of ICG Had Passed ($Retention_{95\%ICG}$) of Rocuronium (n = 3), Vecuronium (n = 3), Org 9487 (n = 3), Org 7617 (n = 3), and *d*-tubocurarine (n = 2), and the Difference in Mean Transit Time (△ MTT) between Muscle Relaxant and ICG

	Retention 95% ICG (%)	ΔMTT (s)
Rocuronium	−6 (−17 − 11)	1.0 (0.8 − 1.4)
Vecuronium	− 11 (−20− 1)	0.2 (−0.8 − 0.3)
Org 9487	10 (−31 − 18)	0.3 (0.2 − 0.4)
Org 7617	−11 (−12 − 8)	0.5 (0.2 − 1.3)
d-tubocurarine	−10 (−3 − −16)	−2.2*
All muscle relaxants	−9 (− − 18)	0.3 (−2.2 − 1.4)

Values are median (range).

* △ MTT −2.2 s in both experiments.

with the exception of the somewhat higher value for Org 7617, which is 3.65.[20] As far as we know, the lipophilicity and protein binding of *d*-tubocurarine are not known. The degree of protein binding of the evaluated muscle relaxants is relatively low to moderate and varies from 0.25 to 0.72.[20] Although a low degree of protein binding increases the amount of drug available for uptake in tissue, opioids with a high degree of protein binding, such as fentanyl and sufentanyl, undergo significant lung uptake.[11,12,21] Other investigators have shown that for opioids the degree of protein binding is not an important factor in determining their pulmonary uptake.[12,21,22] Finally, the initial volume of distribution of these muscle relaxants is close to the plasma volume, suggesting that initially tissue uptake, including lung uptake, is not likely to be extensive.

The high initial (1 and 5 min) concentrations-per-milligram tissue of *d*-tubocurarine, gallamine, and decamethonium found in the lung by Cohen *et al.*[1] in a whole-body autoradiographic study in the rat do not necessarily reflect pulmonary uptake but may be explained by the high blood concentrations and the large amount of blood present in the lung. This corresponds with their finding that the initial concentrations in the liver are also high, but they show a more protracted decay than those in the lung, probably because of subsequent liver uptake.[1]

The peak in the fraction of the muscle relaxant was in some of the experiments somewhat higher than the corresponding peak of ICG, although the time of occurrence was similar or differed by less than 2.4 s. With lung uptake approaching zero, the lung uptake will sometimes be more than zero and sometimes less than zero. Alternatively, a small uptake of ICG cannot be excluded, although ICG is regarded widely as a nonextractable indicator.[19] The somewhat lower ICG peaks cannot be explained by the spectrophotometric measurement of ICG, because the results

of spectrophotometric and high-performance liquid chromatography measurements of samples taken within 20 min after ICG was administered have been similar.[23] The somewhat lower ICG peaks and the slightly negative retention when 95% of ICG had passed may have become overt because no pulmonary uptake of muscle relaxants occurred. In the absence of substantial pulmonary uptake, the differences between the very high concentrations of ICG and muscle relaxants are minimal. Even a small inaccuracy in the measurement of either ICG or muscle relaxant will, according to the aforementioned formula, result in a much larger change in retention than if substantial pulmonary uptake occurs.

The negative values for the difference in MTT between *d*-tubocurarine and ICG were not in accordance to the fraction-*versus*-time curves. The center of gravity of the curve of *d*-tubocurarine in figure 1 is shifted to the right compared with that of ICG, suggesting a positive change in MTT. This discrepancy possibly resulted from extrapolation, which was cumbersome in the case of *d*-tubocurarine, because only four data data points in the descending part of the log-linear curves were available, which affected the accuracy of the calculated MTT of *d*-tubocurarine.

Our anesthetic and analgesic technique was chosen not to restrict any pulmonary uptake of the muscle relaxants. Anesthetics known to be taken up by the lung, such as propofol,[14] or that interfere with the uptake of other compounds, such as propofol[13] and inhalational agents,[13] were avoided. Morphine was selected because it has the lowest pulmonary uptake of all the opioids (4–7%).[11,12]

In conclusion, there is no substantial pulmonary first-pass uptake of rocuronium, vecuronium, Org 9487, Org 7617, or *d*-tubocurarine in pigs. Therefore, differences in pulmonary first-pass uptake do not contribute to the differences in potency and/or onset time among the muscle relaxants.

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